paragraph 2, the Examiner stated:

> Applicant's request for an interview is noted but could not be granted in the time frame desired because upon the filing of a response to the previous Office action, the PTO is required to issue an action within 2 months. Additionally, once a response has been filed, the PTO must respond to the submission and it is not clear what use an interview will have when Applicant has already presented its arguments in writing. These arguments must be responded to in writing, thus an interview is not warranted. If Applicant would like to interview the instant application, it is suggested that a request be made after receiving this Office action and before filing the next response. The request should be made telephonically to either the Examiner of record or to the Supervisory Patent Examiner if the Examiner of record cannot be reached.

1.1. With regard to the Examiner's handling of the November 8, 1999, request for interview, prosecution was simultaneously reopened pursuant to 37 CFR §1.129. MPEP 713.02 states that "a request for an interview prior to the first Office Action is ordinarily granted in continuing or substitute applications".

MPEP 713.01 states that "where the reply to a first complete office action includes a request for an interview, ...the examiner, as soon as he or she has considered the effect of the reply, should grant such request if it appears that the interview or consultation would result in expediting the case to a final action". It also says that "consideration of a filed amendment

may be had by hand delivery of a duplicate copy of said amendment". Plainly, it is possible to hold an interview after an amendment is filed by way of reply to a nonfinal action.

As to the practical question of the value of an interview after amendment, Counsel could, as a consequence of that interview, have filed a supplemental amendment to address concerns not answered by the filed amendment.

1.2. The Examiner failed to examine 63 because it is dependent on a cancelled claim. While that is ground for rejection (MPEP §608,01(n)(V)), the claim should still have been examined on its merits. See 37 CFR §1.104(a)(1) and (b) and MPEP §707.07(g).

1.3. For the reasons set forth above, i.e., the failure to grant an interview and the failure to examine 63 on its merits, the next action, if a rejection, should not be made final.

1.4. The Examiner, SPE Gary Kunz, and BPS Richard Schwartz are thanked for granting Counsel a telephonic interview on June 13.

In the interview, Examiner Saoud suggested replacing the various independent DNA molecule claims (10, 29, 35, 62) with a claim reciting, in the definition of the coding sequence, a "vertebrate growth hormone comprising a deletion or substitution of the amino acid corresponding to Gly119 of bovine growth hormone".

Counsel was assured by the Examiner, at the interview, that the "comprising" indicated that the vertebrate growth hormone in question could be further mutated. However, the interview summary record does not spell this out and, without something on the record to that effect, Counsel is unwilling to trust unreservedly to the new language. Hence, Counsel has retained the prior claims and added the suggested claim as a new claim (79). **With appropriate written assurances from the Examiner, Counsel will cancel the old independent DNA molecule claims.**

Alternatively, the Examiner could call Counsel with a proposed Examiner's Amendment which cancels those claims, to accompany a Notice of Allowance which allows at least new claim 81.

In new claim 81, we recite a "purified or non-naturally occurring DNA molecule comprising a coding sequence encoding a growth hormone receptor antagonist". Merely reciting a "vertebrate growth hormone" would imply that the mutant polypeptide promoted growth. (For the same reason, we retain the recitation "said polypeptide having growth hormone receptor antagonist activity".)

Next, we recite that this antagonist is "a mutant polypeptide comprising an amino acid sequence". This gives antecedent basis for later references to the sequence.

Next, we recite "said polypeptide being a mutant of a vertebrate growth hormone". We have already explained why this is better than referring to the polypeptide as being a "vertebrate growth hormone".

Then we say that the amino acid sequence of the mutant is one "comprising a substitution of the glycine corresponding to Gly119 of bovine growth hormone". This is almost the same as the examiner's language, but we thought it better to make clear that the original amino acid was a glycine. Also, we thought it desirable to specify that it was substituted with "an amino acid other than glycine or alanine", as we taught against the Gly→Ala substitution. While we can live with "substituted", we would prefer to say "replaced". We consider "substitution" to be the result of the replacement.

We have retained the final proviso of claim 10, intended to deal with possible inherent anticipation by Cunningham. The Cunningham proviso does not raise a "description" issue since Cunningham's mutant is disclosed in the specification (see page 16, line 34 to page 17, line 7, and the incorporation by reference at page 55, lines 22-23). We have a right to excise

it pursuant to In re Johnson, 194 USPQ 187 (CCPA 1977), as was conceded orally at the interview.

Since the Examiner indicated that, if the Cunningham mutant is referred to in the claim, it is "essential" material, and its incorporation by reference is improper, we have inserted Cunningham's Table 1 at page 17, line 1 as new Table A. In addition, we have amended the specification to similarly insert the alanine substitution data from the incorporated-by-reference article cited at page 17, lines 14-15, as new Table B.

The captions immediately following these tables are also taken from the aforementioned articles.

New claims 82-85 are plainly based on page 18, lines 6-10. New claim 106 is based on page 14, lines 10-13. New claims 86 and 87 are plainly based on page 17, line 35 to page 18, line 2. See also original claim 6.

New claims 88 to 98 are method claims paralleling 46-56 but dependent on new claim 81. Note that these claims do not require an effect on a disease. They merely require reduction of growth hormone activity in the subject. The subject may be one who suffers from a particular disease.

New claim 99 is an alternative approach to the "Upjohn" issue (see 3.8 below); it disclaims the G119P embodiment expressly set forth at page 51, line 20; see also original claims 2-4 and 7-9. New claims 100-104 are also based on original claims 2-4 and 7-9. New claim 105 is based on original claim 5 and on page 24, lines 1-15.

2. Definiteness

2.1. The Examiner says that the term "reference vertebrate growth hormone" is not defined and does not have a well-known art recognized meaning.

This term was accepted in previously issued claims. The term has a common sense meaning: it is a naturally occurring

vertebrate GH which is used as a "reference." This is exactly how hGH and bGH are used on page 13, line 33 and page 14, line 13; bGH on page 14, lines 19-24, pGH, bGH and hGH on page 15, lines 1-18; bGH again on lines 19-24; flounder GH on page 15, line 35 to page 16, line 28; several GHs on page 17, lines 16-22; bGH and hGH again on line 33; and bGH on page 18, lines 4-12, 29 and 37.

Nonetheless, to expedite prosecution, "reference" has been deleted. The recitation of "first vertebrate growth hormone" should be adequate for identification, so "reference" was actually redundant.

2.2. While the requirement is rather pedantic, claim 39 has been amended to make it explicit that the reference vertebrate GH is bovine GH.

3. Description/New Terminology (OA §6)

The Examiner has made two separate "description" rejections, in OA § 6 and § 7. In this section, we will only address OA § 6.

3.1. The first issue is whether the specification "described" a protein which is at least 50% identical to a "first reference vertebrate growth hormone."

The Examiner concedes that the specification discloses (1) "proteins which are substantially homologous with a vertebrate GH but have growth inhibitory activity," (2) a polypeptide having an alpha helix which is at least 50% identical with the third alpha helix of a vertebrate GH, and (3) that bGH is 66% identical to hGH.

Let us first examine the meaning of "substantially homologous." The specification expressly teaches that "all non-bovine vertebrate GHs are substantially homologous with bGH and/or hGH" (page 18, lines 4-6). The mammalian GHs (a subset of vertebrate GHS) mentioned at page 14, lines 19-21 are 66-99%

identical to GH." The percentage identity of bGH with fish GHs is not stated explicitly, but typically these lie in the mid-30s. See Watahiki, et al. (1989) and references cited therein.

With regard to "50%" referring to the alpha helix, not the entire sequence, we respectfully refer the Examiner's attention to page 18, lines 6-12:

> "Preferably, the polypeptide is at least about 50% homologous, more preferably at least 80% homologous, with bGH or hGH in the subsequence substantially corresponding to the third alpha helix (approximately, residues 106-129) of bGH, and more preferably over the entire length of the polypeptide (ignoring extraneous non-bGH-related fusions to the amino-terminus or carboxy-terminus). [emphasis added]

However, even in the absence of this explicit teaching, it is clear from page 14, lines 19-24 that among real world polypeptides, the degree of identity in the third alpha helix is a good predictor of the overall identity:

vs. bGH	helix 3	overall
porcine	94	92
ovine	94	99
human	66	66
rat	94	87

3.2. With regard to support for "66%," "88%," and "90%," the "66%" is based on the similarity of hGH and bGH. It is clear that bGH and hGH are both "substantially homologous" and 66% identical. Applicants clearly contemplated that a vertebrate GH other than bGH could serve as the "scaffolding" for mutation, and that this other GH could be hGH. The parallel hGH mutant would be 66% identical to the bGH mutant, as in the case of hGH G120R

and bGh G119R.(See Tables). One could also introduce the same mutation into an hGH/bGH chimera, and this would have a higher than 66% identity to either bGH or hGH. Chimeras of mammalian GHS are disclosed at page 25, lines 17-21. Moreover, a parallel mutant of another mammalian GH, such as pGH, could be more than 66% identical to bGH.

The description requirement does not require that every claim limitation exactly echo the specification. Ralston Purina Co. v. Far-Mar Co., Inc., 222 USPQ 863, (D.Kan. 1984), aff'd in part and rev'd in part, 227 USPQ 177 (Fed. Cir. 1985). The Federal Circuit held that a total moisture content limitation of "at least about 25%" was supported by the express disclosure of soybean meal with 10-12% water and addition of 25% or 27% water, for total content of 35-39%. The limitation of "protein content of at least about that of solvent extracted soybean meal" (which was 50%) was supported by the disclosure that meals of 44%, 50%, 70% and 90% protein were standard. The limitations of temperature of "in excess of 212°F" and "into the range of 212-310°F" were supported by the disclosure of 212-380 in Example 1. In Kolmes v. World Fiber Corp., 41 USPQ2d 1829 (Fed. Cir. 1997), the claim to a rate of 8-12 turns per inch was supported by the disclosure of 4-12, with 8 being preferred.

With respect to "80%," the basis for this number is explicit, at page 18, lines 7 and 10.

Support for "90%" is not explicit. However, the specification discloses rat and porcine GH as reference GHs. These are 87% and 92% identical to bovine GH, per page 14, lines 19-21. Hence, "90%" is a compromise value. We would be willing to replace "90%" with "87%" or "92%" if that would alleviate the Examiner's concerns.

3.3. In claim 10, (B)(II)(b)(ii), we have the limitation that the binding affinity of an Ala substitution mutant of the reference GH is at least 10% that of the wild-type reference GH.

The Examiner mistakenly assumes that the affinity might be determined using a receptor other than the GH receptor. The paragraph explicitly refers to the "reference vertebrate growth hormone's receptor."

With regard to the value "10%," this was based on page 19, lines 30-34. An ED50 10 times the wild-type ED50 implies an affinity which is 10% of the wild-type affinity.

3.4. Claim 19 does not require that all residues outside GD1-GD5 be mutated non-conservatively. Rather, it limits the location of the non-conservative substitutions, if any, to positions outside GD1-GD5. Similarly, considerations apply to th recitation of "non-conservative substitution" in claim 20-24. **Claims 19-24 have been amended to insert --, if any,-- after "non-conservative substitution."**

3.5. We disagree with the Examiner's comments concerning claim 29 (at least 50% identity in residues 96-133). We have already identified the basis for "50%." With respect to "96-133," see page 17, line 29 to page 18, line 3:

> "The concept of a polypeptide which is substantially homologous to bGH is deemed to include (but is not limited to) any polypeptide which differs from bGH or hGH by (a) a substitution (or deletion) at an amino acid corresponding to amino acids 115 to 119 of bGH, (b) a substitution (or deletion) at an amino acid corresponding to an amino acid of bGH or hGH which is not conserved among the vertebrate GHS, especially the replacement of that amino acid by one found at the site in a different GH, and/or (c) truncation of amino acids 1-95 and/or 134-191."

Since bGH is 191 a.a. long, truncation of both "1-95" and "134-191" would of course leave "96-133."

3.6. Claim 34 recites an ED50 limitation based directly on page 19, lines 30-34.

3.7. With respect to the "Cunningham proviso," excluding

a specific mutant, the Examiner made a similar rejection on April 10, 1998, right after the proviso was introduced. The reason for the exclusion was fully explained in the Amendment of January 22, 1998, pp. 12-14, and the legal basis for the excission of prior art was set forth on pp. 11-13 of the September 10, 1998, Amendment (together with further comments on how the proviso distinguished Cunningham).

The rejection was not repeated in the November 6, 1999 action, and hence, by virtue of § 3 thereof, was withdrawn. We do not understand why it is being reinstated now, and why the Examiner does not respond to our September 10, 1998 remarks.

3.8. With regard to the "other than proline" limitation of claim 37, the motivation for the exclusion of Pro was the reference to the mutation hGH G120P in the UpJohn Patent. Under In re Johnson, 194 USPQ 187 (CCPA 1977) this is a sufficient basis for excising Pro.

Another reason is that Pro, next to Gly, is the AA least favorable to alpha helix formation. Compare page 21, lines 3-8 with page 24 (Gly at 0.53, Pro at 0.59; in contrast, Leu at 1.34, Lys at 1.07, Arg at 0.79 and Trp at 1.14). Note that at position 115, we said that "His, Met, Leu and Trp are more preferred because they combine the advantages of bulk with a reasonable strong alpha helical propensity". So, in a normally helical region, substitutions with low alpha helical propensities are less preferred.

Gly is, of course, the smallest of the 20 amino acids. The importance of the size of the replacement amino acid is set forth generally at page 21, lines 3-28. At lines 24-25, it suggests that this position be occupied by an A.A. "at least as large as Pro" (the third smallest replacement A.A. known to result in a small animal phenotype).

If "at least as large as Pro" is preferred, even larger would be more preferred. **New claim 80 recites "at least as large**

as Leu" since Leu is the next largest successful replacement, see page 24.

3.9. With respect to the "greater alpha helical propensity" language of claim 38, there is basis not only at page 22, lines 11-14, but also at page 23, lines 17-21; page 13, line 34; page 19, lines 20-25; page 20, lines 32-35.

4. Description/Representative Species (OA §7)

The revised written description guidelines set up a framework for determining whether a "genus" claim to a DNA or a polypeptide is adequately described.

According to both the original 1998 and the revised 1999 "written description" guidelines, for a "genus" to be adequately described, a "representative number of species" must each be adequately described according to the criteria discussed in connection with species claims. This could be a mix, with some species described by a "complete structure", and others by an assemblage of characteristics, or by a combination of function/structure-function correlation. How many is enough? The Guidelines said:

> What constitutes a "representative number" is an inverse function of the predictability of the art.... The number must be sufficient to reasonably identify the other members of genus.

A species claim (or a species of a genus claim) satisfies the description requirement if (1) a "complete structure is disclosed" (the PTO calls this a "safe haven")[1], or (2) "the specification discloses other relevant identifying characteristics, i.e., physical and/or chemical characteristics and/or functional characteristics coupled with a known or

[1] The revised guidelines refer to an "actual reduction to practice" or a "reduction to drawings" of a "complete structure."

disclosed correlation between function and structure, sufficient to describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize applicant was in possession of the claimed invention". In judging whether criterion (2) was satisfied, the PTO would consider the "level of predictability" in the art: "For example, if there is a well-established correlation between structure and function in the art, one skilled in the art will be able to reasonably predict the complete structure of the claimed invention from its function". The PTO went so far as to concede that "in some factual situations, the written description requirement may be satisfied through disclosure of function alone when there is a well-established correlation between structure and function".

The revised Guidelines remark:

> Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient.

Reviewing the specification, we find that the following species are described by a <u>complete structure</u> that was actually reduced to practice:

bGH G119R

bGH G119P[2]

---

[2] While bGH G119P <u>per se</u> is excluded from the DNA claims, it is still relevant to species which combine the G119P mutation with other mutations, such as E117L and A122D.

bGH G119K

bGH G119L
bGH G119W
bGH E117L/G119R/A122D

hGH G120R
hGH G120W

The next question is whether those species are representative of the claimed genus.

The claims limit both the overall level of sequence variation (must include a sequence at least 50% identical to a reference vertebrate GH) and the location and nature of the individual mutations (mutations at a given site must either be conservative, or justified by Ala scanning mutagenesis or by tolerance of mutation at that site in naturally occurring vertebrate GHs). The claims also require that the variation be compatible with retention of GH receptor antagonist activity.

The Examiner's attention is respectfully directed to Example 14 of the examiner training materials. Its claim covers "a protein having SEQ ID NO:3 and variants thereof that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A→B". An assay for the enzymatic activity in question is described, and the procedure for making variants (e.g., site-specific mutagenesis of the corresponding DNA) is conceded to be conventional. The PTO concluded that because of the structural (95% identity) and functional (catalytic activity) limitations, the genus "does not have substantial variation". Hence, the PTO said that it would hold the single disclosed species to be representative of the genus.

Here, the percentage identity limitation (of the main claim) is laxer (50%), but there are also more supporting species. The

species bGH G119R and hGH G120R are only 66% identical, and it is known in the art that pairs of vertebrate GHs exist which are less than 40% identical, although they share growth promoting activity. There is a known and disclosed correlation between activity and structure for the vertebrate GH activity, and conserved and nonconserved positions have been identified by studies of both naturally occurring variations and the effects of alanine scanning mutagenesis. There is also a generally accepted correlation, for homologous proteins generally, between the similarity of the exchanged AAs in size, hydrophilicity, etc., and the likelihood that the replacement will be tolerated. The claims are carefully tailored with these teachings in mind.

It is worth pointing out that the training example claim was interpreted as meaning that the protein must comprise a sequence at least 95% identical to SEQ ID NO:3. The protein as a whole need not be 95% identical to SEQ ID NO:3, it may be larger (perhaps much larger) than SEQ ID NO:3. While there could be considerable variation in the additional N- or C-terminal sequences, the Training Materials implied that this potential variation is not considered significant, perhaps because of the functional limitation and the ability of the required core sequence to provide that function.

This is consistent with training example 8, where the hypothetical claim is to "an isolated and purified nucleic acid comprising SEQ ID NO:2". Even though this claim is in open form, it is said to be adequately described.

The genus was directly supported by a single explicitly disclosed species (SEQ ID NO:2) which was actually reduced to practice. As to the other species in the genus, the training materials comment

> One of skill in the art can readily envisage nucleic acid sequences which include SEQ ID NO:2 because e.g. SEQ ID NO:2 can be readily embedded in known vectors. Although there may be substantial variability among the

> species of DNAs encompassed within the scope of the claim because SEQ ID NO:2 may be combined with sequences known in the art, e.g. expression vectors, the necessary common attribute is the ORF (SEQ ID NO:2).
>
> Weighing all factors including (1) that the full length ORF (SEQ ID NO:2) is disclosed and (2) that <u>any substantial variability within the genus arises due to addition of elements that are not part of the inventor's particular contribution</u>, taken in view of the level of knowledge and skill in the art, one skilled in the art would recognize from the disclosure that the applicant was in possession of the genus of DNAs that comprise SEQ ID NO:2. [emphasis added]

Example 9 deals with a claim to "an isolated nucleic acid that specifically hybridizes under highly stringent conditions to the complement of the sequence set forth in SEQ ID NO:1, wherein said nucleic acid encodes a protein that binds to a dopamine receptor and stimulates adenylate cyclase activity".

Hybridizing nucleic acids <u>were</u> isolated, but <u>not</u> sequenced. The conclusion is favorable to the applicant:

> turning to the genus analysis, a person of skill in the art would not expect substantial variation among species encompassed within the scope of the claims because the highly stringent hybridization conditions set forth in the claim yield structurally similar DNAs. Thus, a representative number of species is disclosed, since highly stringent hybridization conditions in combination with the coding function of DNA and the level of skill and knowledge in the art are adequate to determine that applicant was in possession of the claimed invention.

With regard to coverage of fragments of full-length GH, Applicants wish to call attention to training example 15, dealing with an antisense claim: "An antisense oligonucleotide complementary to a messenger RNA having SEQ ID NO:1 and encoding

human growth hormone, wherein said oligonucleotide inhibits the production of human growth hormone". [3]

The claimed genus was supported by a single species with a complete structure (the full-length complement of ID 1). The genus included fragments of this complement. The trainers comment,

> It is generally accepted in the art that oligonucleotides complementary to a messenger RNA, including fragments of the full-length complement, have antisense activity when they match accessible regions on the target mRNA. Generally, the close the complementary fragment is to full length, the greater the likelihood it will have antisense activity. In addition, oligos that retain complementarity to the Shine-Delgarno sequence usually have antisense activity.

Hence, it is clear that the claims satisfy the "written description" requirement.

Respectfully submitted,

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[3] The Example is of general interest as an illustration of "implicit" description: "one of skill in the art would view applicant's disclosure of a coding sequence, with the statement that the invention includes antisense oligonucleotides, as an implicit disclosure that the full-length complement of SEQ ID NO:1 is an antisense oligonucleotide".